Notch1 represses osteogenic pathways in aortic valve cells.

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Public Summary:
Calcific aortic stenosis is the third leading cause of adult heart disease and the most common form of acquired valvular disease in developed countries. However, the molecular pathways leading to calcification are poorly understood. We reported two families in which heterozygous mutations in a gene called NOTCH1 caused severe aortic valve calcification and bicuspid aortic valve, a condition in which the aortic valve has only two leaflets instead of three. NOTCH1 is part of a highly conserved signaling pathway involved in cell fate decisions, cell differentiation, and cardiac valve formation. In this study, we examined the mechanism by which NOTCH1 represses aortic valve calcification. Mice that were missing one copy of the Notch1 gene had greater than fivefold more aortic valve calcification than control mice of the same age and sex. Inhibition of Notch signaling in cultured sheep aortic valve interstitial cells (AVICs) also increased calcification more than fivefold and resulted in gene expression typical of osteoblasts, which are cells responsible for bone formation. We found that Notch1 normally represses the gene encoding bone morphogenic protein 2 (Bmp2) in mouse aortic valves in vivo and in aortic valve cells in vitro. A genetic modification technique known as siRNA-mediated knockdown of Bmp2 blocked the calcification induced by Notch inhibition in AVICs. These findings suggest that Notch1 signaling in aortic valve cells represses osteoblast-like calcification pathways mediated by Bmp2.

Scientific Abstract:
Calcific aortic stenosis is the third leading cause of adult heart disease and the most common form of acquired valvular disease in developed countries. However, the molecular pathways leading to calcification are poorly understood. We reported two families in which heterozygous mutations in NOTCH1 caused bicuspid aortic valve and severe aortic valve calcification. NOTCH1 is part of a highly conserved signaling pathway involved in cell fate decisions, cell differentiation, and cardiac valve formation. In this study, we examined the mechanism by which NOTCH1 represses aortic valve calcification. Heterozygous Notch1-null (Notch1(+/)(-)) mice had greater than fivefold more aortic valve calcification than age- and sex-matched wildtype littermates. Inhibition of Notch signaling in cultured sheep aortic valve interstitial cells (AVICs) also increased calcification more than fivefold and resulted in gene expression typical of osteoblasts. We found that Notch1 normally represses the gene encoding bone morphogenic protein 2 (Bmp2) in murine aortic valves in vivo and in aortic valve cells in vitro. siRNA-mediated knockdown of Bmp2 blocked the calcification induced by Notch inhibition in AVICs. These findings suggest that Notch1 signaling in aortic valve cells represses osteoblast-like calcification pathways mediated by Bmp2.